Intestinal permeability and autoimmune diseases

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Exact aetiology of most autoimmune diseases is unknown. Genetic predisposition, environmental factors, microbiota dysbiosis and the gut–brain axis are known to interplay in autoimmune disease development. Arresting such interplay, by implementing a particular diet (such as the low FODMAP diet) or by consuming specific drugs (such as zonulin antagonists) for example, will reduce disease symptoms, reverse intestinal hyperpermeability and allow remission. The aim of this study was to investigate possible mechanisms of autoimmune disease aetiology and alterations in intestinal permeability, specifically in coeliac disease and type 1 diabetes mellitus. This was done by collecting researched evidence from journals and other publications. Understanding the pathology of the diseases and identifying the particular genes and triggers involved as well as improving investigative methods will potentiate the development of prevention and treatment therapies.

Methods: Collection of researched evidence was conducted from journals and other publications.

Key words: intestine, permeability, autoimmune, coeliac, diabetes, zonulin

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Introduction

When the body’s ‘great protector’, the immune system, goes amiss, autoimmunity, the state in which the body attacks itself, ensues. Autoimmune diseases are characterized by tissue damage and loss of function arising from abnormal immune response directed against specific organs. Such diseases are chronic and debilitating, brutally reducing quality of life. More than 80 types of autoimmune disorders are known to exist and a rise in both incidence and prevalence of the disorders has induced increased scientific interest. Although aetiology of autoimmune diseases is unknown, genetic predisposition, environmental factors, gut microbiota dysbiosis and defective bidirectional gut–brain communication have been identified as possible contributors (Campbell, 2014).

Several genes encoded by the major histocompatibility complex (MHC) have been identified to predispose individuals to certain autoimmune diseases, suggesting that common immunological pathways may be involved. The observation that CTLA4 and PTPN22 are associated with various autoimmune diseases is consistent with the hypothesis that certain immunological pathways are common in multiple diseases whereas others are specific to a particular disease (Rioux and Abbas, 2005). Identifying a particular gene associated with a disease allows immunologists to investigate and better understand the pathways and molecular mechanisms, vital for developing a cure. However, genetic predisposition only accounts for 10–40% of cases suggesting environmental factors and microbiota health play greater roles.

Chemical toxins, bacteria, viruses, emotional stress and drugs are environmental triggers potentially leading to autoimmune disorders. Metals such as aluminium hydroxide, nickel and cobalt may induce inflammation by activation of pattern recognition receptors. Aluminium hydroxide used in
vaccines (for example, the hepatitis B vaccine) and medical silicons used in breast implants have shown to elicit Shoenfeld’s syndrome (Hamza et al., 2012, Vera-Lastra et al., 2012). However, environmental factors are not necessarily the inducers but may cause amplification of an existing autoimmune disease or cause relapse (Campbell, 2014).

The inducer of autoimmune responses related to the gut is most likely to be microbiota dysbiosis leading to increased intestinal permeability. The condition of the gut flora is influenced by diet, mucosal health and the gut–brain axis. The human diet has changed substantially over the years, from eating food shortly after harvest and in season with only occasional consumption of meat, to eating what we want when we want, and in no modest amount. The food itself has been dramatically transformed. New strains of grains engineered to resist pathogens and herbicides is one of many examples. Everyday consumption of genetically modified or processed food is inevitable. Maintaining a wholesome and balanced diet is essential in ensuring healthy gut microbiota for correct gut–brain communication and overall health.

Over one hundred trillion microorganisms, including one thousand different species of microbes encompassing more than 3 million genes, reside in human gut microbiota (Jandhyala et al., 2015). While an individual’s microbiota is unique, evolving from birth to old age as well as being environmentally influenced, it realizes the same physiological function in all humans, that is, protection. The microbiota offers protection by repressing pathogenic growth and prevention against allergy and disease by regulating the immune system (Guarnier and Malagelada, 2003). It ensures the passage of non-harmful molecules via the intestinal epithelium by providing barrier fortification, appropriate mucous composition and apical tightening at tight junctions (TJs).

Complex and bidirectional, the communication pathways between the gut microbiota and the brain play an important role in human health and disease. Mutualistically associated, the gut hosts an environment potentiating microbiota growth, while microbiota maintains homeostasis within the body and overall health. Gut–brain and brain–gut communication occurs by means of neural (autonomic and enteric nervous systems), endocrine, metabolic and immune systems (Zhou et al., 2015). Disruption of one such system may have pathological consequences.

Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial layer preserves the equilibrium between tolerance and immunity to non-self-antigens, preventing pathology and minimizing inflammation. Permeability of this layer is therefore responsible in maintaining this balance. Increased permeability is thought to be triggered by several parties and mechanisms such as bacterial endotoxins (acquired from bacterial infection or genetically modified organisms) causing disruption of actomyosin networking leading to epithelial cell damage and stress-induced zonulin eliciting tight junction damage (Campbell, 2012).

Tight junctions

The intestinal epithelium is the largest mucosal surface present in the human body (~7.5 m) and provides an interface between the internal and external environments. Comprising of a single layer of epithelial cells interconnected by dynamic intercellular junctions along their lateral margins, the epithelium orchestrates the locomotor, digestive, absorptive, neuroendocrinological and immunological functions of the intestine. Exchange between the intestinal lumen and submucosa of proteins can occur via two mechanisms: transcellular transport (via endo-/exocytosis) and paracellular transport (via TJs) subject to molecular weight. Molecules sized 10–15 Å are transported paracellularly, meaning ‘side’ cells, through modulation of TJs. Macromolecules greater than 15 Å however are too large and are not trafficked across the epithelial layer in the presence of competent TJs (Fasano, 2008). Malfunctioning TJs due to incorrect assembly will therefore cause intestinal hyperpermeability with noxious effect.

TJs are composed of integral proteins, including occludin, claudins and junctional adhesion molecules (JAMs), and cytoplasmic plaque junctional complex proteins (ZO-1, ZO-2, ZO-3, 7H6, symplekin and cingulin). Tight junctions are bound to and interact with the apical actomyosin rings made up of cellular cytoskeleton structures. Assembly occurs via a cascade of biochemical events ultimately leading to a complex of exquisite anatomy and function. Opening and closing of epithelial TJs is dependent on various stimuli including dietary intake, neural and endocrine signals, and immunological factors such as inflammatory mediators and mast cells (Arrieta, Bistritz and Meddings, 2006).

Many bacteria enhance permeability of the epithelial layer by altering TJ state presumably for the benefit of their own growth. Vibrio cholerae was studied by Fasano (1999), a gastroenterologist from the University of Maryland, who uncovered the bacterium’s mechanism of increasing paracellular permeability by the release of toxins, one of which is named Zonula occludens toxin (ZOT), which binds to apical membrane receptors on the enterocyte activating a cascade of intracellular events resulting in actomyosin contraction and TJ disassembly. Since it is unlikely that this pathway existed for the sole benefit of bacteria, Fasano and his team speculated that the pathway was a physiological one which bacteria had evolved to take advantage of. Several years later this was proven to be correct as the human homologue, zonulin, was identified using affinity-purified anti-ZOT antibodies and a chamber assay in foetal and adult human intestine (Wang et al., 2000). The physiological role of zonulin and the zonulin system is still in question. However, it is presumed to play a pivotal role in tissue morphogenesis, movement of fluid, macromolecules and leukocytes between the intestinal lumen and the interstitium, protection against microorganism colonization and pathological processes including inflammation, autoimmunity and cancer.
Fasano and his team proposed a zonulin signalling pathway: zonulin activates epidermal growth factor receptor (EGFR) directly through EGFR-binding or indirectly via transactivation of EGFR (Zonulin binds to protease-activated receptor 2 (PAR2) followed by Src or matrix metalloproteinase/a disintegrin and metalloproteinase (MMPs/ADAMs) mediated Pro-HB-EGF activation which in turn activates EGFR). EGFR activates phosphokinase C (PKC) which hydrolyses phosphatidylinositol (PPI) releasing inositol 1,4,5-trisphosphate (PPI-3) and diacylglycerol (DAG). DAG activates PKCα directly by binding to it while PPI-3 indirectly activates PKCα via intracellular Ca\(^{2+}\) release. Activated PKCα catalyses the phosphorylation of target proteins ensuing polymerization of G-actin and F-actin. This causes the actin filaments to rearrange which displaces junctional complex proteins such as ZO-1 and ZO-2 loosening the TJ and allowing the exchange of appropriately sized molecules. Once zonulin signalling is ceased, the TJ returns to its closed baseline state.

Zonulin is the only described physiological modulator of intercellular TJ arrangement in humans. Deregulation or disruption of the zonulin signalling pathway in genetically susceptible individuals is hypothesized to lead to increased intestinal permeability and possible autoimmune disorders. The classic paradigm of autoimmune disorders, involving specific gene makeup, microbiota dysbiosis, incorrect communication between innate and adaptive immunity and exposure to environmental factors, has had to make room for a new element, that of loss of junction of the intestinal barrier due to TJ displacement. Intestinal hyperpermeability is often found to precede autoimmune disorders and is suspected to be the means by which abnormal passage of antigens from the intestinal lumen results in an autoimmune response. This novel theory is encouraging as it implies autoimmunity is non-auto perpetuating and suggests the possibility of prevention or treatment of autoimmune disorders by arresting the interplay between genes and environmental triggers through intestinal barrier function re-establishment, a new and innovative approach to treatment (Fasano, 2012a).

Safety and efficacy testing of zonulin inhibitor, larazotide acetate (AT-1001), are currently being carried out. Results from experiments using BioBreeding diabetes-prone (BBDP) rats prove promising. Larazotide acetate administration to BBDP rats prevents disrupted intestinal barrier function, autoantibody production, pancreatic islet destruction and disease development (70% decrease in diabetes incidence) (Watts et al., 2005, Fasano, 2011). It has also shown to be effective in managing coeliac disease. In an experiment carried out by Leffler et al. (2015), coeliac disease suffers orally administered with larazotide acetate experienced reduced symptoms within weeks of administration (50% reduction in abdominal pain reported). This inhibitor is the first of a novel class of agents targeting permeability through TJ regulation and may soon be considered an important therapeutic option for autoimmune disease sufferers. More experiments are currently being effectuated to contribute to the growing evidence for the drug’s safety and efficacy.

**Results**

**Coeliac disease**

Coeliac disease is an autoimmune enteropathy resulting from inappropriate T-cell-mediated immune responses to ingested gluten contained in grains such as wheat, barley and rye. Gliadin is the toxic component of gluten and is responsible for intestinal damage. In the continuous presence of gliadin, the disease is self-perpetuating. Other coeliac disease symptoms include autoimmune targeting of tissue transglutaminase (tTG) and association with the major histocompatibility complex (MHC) haplotypes. Coeliac disease is strongly associated with the human leucocyte antigen (HLA) gene with over 90% of patients carrying the HLA-DQ2 haplotype while the remainder carry HLA-DQ8 (Lammers et al., 2008).

Under normal physiological conditions, access of gliadin to submucosal tissue is prevented by competent TJs limiting passage of macromolecules. In individuals carrying the HLA-DQ2 or -DQ8 haplotypes however, TJs are disassembled allowing permeation of gliadin and triggering gliadin-induced immune responses eventually leading to pathology associated with coeliac disease (Lammers et al., 2008). Autoimmunity is believed to be triggered via a succession of events following gluten ingestion. Upon reaching the intestinal lumen, gliadin and its immunomodulatory and inflammatory fragments bind to chemokine C-X-C receptor 3 (CXCR3) inducing myeloid differentiation primary-response protein 88 (MyD88) dependent zonulin release resulting in disassembly of TJs. Following removal of the functional amide group by tTG, gliadin peptides, having crossed the epithelium through opened TJs, bind to HLA molecules on the antigen-presenting cell surface (APC). This triggers the release of My88-dependent Zonulin and cytokines. HLA-gliadin peptide complexes presented by APCs cause T-lymphocyte activation of both humoral (B cell activation leading to plasma cell release of anti-gliadin antibodies (AGA), N-arachidonylethanolamide (AEA) and anti-tissue transglutaminase (tTG) and cell-mediated (natural killer cells which destroy epithelial cells via cytokine release) responses.

The interplay between the two responses (innate and adaptive) ultimately leads to the autoimmune process leading to coeliac disease. Once gluten is no longer part of the individuals diet, gliadin is no longer present, zonulin blood levels decrease and TJs become competent once again. The intestinal epithelium resumes its normal functioning, autoantibody levels return to normal, the autoimmune response is shut-off and consequently, intestinal repair occurs and thus complete remission ensues.

In an experiment by Fasano and his team (Fasano, 2012b) intended to measure possible zonulin perturbation during...
coeliac disease, intestinal tissue was obtained from seven individuals suffering from coeliac disease and six non-sufferers. These were probed for zonulin with anti-zonula occludens toxin (ZOT) antibodies. Immunofluorescence studies and quantitative immunoblotting of coeliac diseased tissues showed increased zonulin expression and higher zonulin protein concentrations in the intestinal submucosa which was absent in control tissues. Since zonulin levels have been found to be elevated in individuals with coeliac disease in the acute phase, when TJs are open, this suggests zonulin as the key mediator in the pathology of coeliac disease. Further, an increase in expression as a result of TJ displacement may provide increased zonulin presentation to immune cells in the submucosa thus resulting in an autoimmune response. To verify this hypothesis, ZOT-based ELISA was used to measure zonulin antibody levels in the blood of coeliac disease sufferers against a control group. While anti-zonulin IgG levels were similar in patients with coeliac disease and in controls, anti-zonulin IgA levels were elevated in 21% of coeliac diseased patients during the acute phase of the disease. In remission, individuals’ anti-zonulin IgA levels and intestinal permeability returned to normal after 3–6 months on a gluten-free diet, further evidencing zonulin as the main contributor to disrupted barrier function.

Irish setter dogs were used in an experiment to provide evidence for increased intestinal permeability participating in the aetiology of coeliac disease (Hall and Batt, 1991). The litters were bred from gluten-sensitive enteropathy suffering dogs. The experiment compared litters predisposed to disease reared on a gluten-free diet and on a normal diet, compared to a control group of healthy dogs on a normal diet. Permeability was found to have risen in the litters on a gluten-free diet with unaffected intestinal integrity. In litters reared on a normal diet, increased intestinal permeability was noted compared to that in gluten-free diet litters after just 4 months and elicited villus degeneration, intraepithelial lymphocyte infiltration and reduced ALP activity. The findings support the hypothesis that intestinal hyperpermeability is a primary defect involved in eliciting gluten-sensitive enteropathy in Irish setter dogs. It is important to note however, that the gluten-free diet may have contained other elements potentiating sensitivity. Carrageenan is an additive often found in dog gluten-free diet may have contained other elements potentiating increased intestinal permeability in the intestinal submucosa which was absent in control tissues. Since zonulin levels have been found to be elevated in individuals with coeliac disease in the acute phase, when TJs are open, this suggests zonulin as the key mediator in the pathology of coeliac disease. Further, an increase in expression as a result of TJ displacement may provide increased zonulin presentation to immune cells in the submucosa thus resulting in an autoimmune response. To verify this hypothesis, ZOT-based ELISA was used to measure zonulin antibody levels in the blood of coeliac disease sufferers against a control group. While anti-zonulin IgG levels were similar in patients with coeliac disease and in controls, anti-zonulin IgA levels were elevated in 21% of coeliac diseased patients during the acute phase of the disease. In remission, individuals’ anti-zonulin IgA levels and intestinal permeability returned to normal after 3–6 months on a gluten-free diet, further evidencing zonulin as the main contributor to disrupted barrier function.

By chance, Fasano (2011) uncovered the key to unlocking the means of oral delivery of large-molecule drugs across the intestinal epithelial layer. Earlier attempts to open up TJs between epithelial cells failed due to the complete and irreversible destruction of the TJ, differing from zonulin’s valuable reversible displacing effect. In early studies, Fasano showed ZOT’s ability to induce a 10-fold increase in insulin absorption and six-fold increase in absorption of immunoglobulins in rabbit small intestine (Fasano and Uzzau, 1997). Diabetic rats were also studied, where ZOT administration demonstrated a greater decreased in blood glucose levels compared to those derived following insulin injections. This opens up the possibility of replacing painful insulin injections with oral pill ingestion. The oral delivery of drugs such as taxol and growth hormone in conjunction with zonulin could, for example, be considered for treating cancer. The discovery may also change the lives of many autoimmune disease sufferers. Knowing that increased permeability of TJs predisposes individuals to autoimmune diseases suggests that with appropriate permeability reinstated, likelihood of disease development is reduced.
The discovery of zonulin, a potential tool for drug and peptide transport through the intestinal epithelium, is tremendously exciting. ZOT displays many useful properties making it a suitable candidate for the job: it is non-cytotoxic; it does not irreversibly destructs the epithelium, but rather, displaces TJIs in a reversible manner; it interacts with a region-specific receptor (specific to jejunum and distal ileum); it is not effective in the colon where it could potentiate harm via intestinal barrier disruption; it does not induce acute systemic side effects; and it acts relatively quickly (increased permeability detected 20 min after oral administration).

**Type I diabetes mellitus**

Type 1 diabetes mellitus (T1D) is defined by hyperglycaemia instigated by an autoimmune destruction of insulin-producing β-cells in the pancreas. Various genes have been identified to be involved in T1D susceptibility. The main two are the HLA gene region IDDM1, located on chromosome 6p21 and accounting for 42% of genetic susceptibility, and the insulin gene region IDDM2, on chromosome 11p accounting 10% of genetic susceptibility. Other known chromosomal locations with undetermined susceptibility genes have been described (Kelly et al., 2003). Additionally, polymorphisms in MYO9B, a gene involved in intestinal permeability have also shown interrelation with T1D development (Santiago et al., 2008).

Subjected to particular environmental triggers, genetically predisposed individuals may develop T1D. Such triggers have yet to be identified, and would allow for prevention and treatment of the disease. Gliadin is believed to be a T1D trigger, its mechanism similar to that in coeliac disease. Non obese diabetic (NOD) mice and BBDP rats have been used to demonstrate that gliadin is a dietary trigger for T1D showing increased intestinal permeability following wheat administration. Rearing NOD mice and BBDP rats on a gluten-free diet resulted in delayed and reduced T1D development. The study also showed that time of exposure to the trigger is important: delayed gluten exposure by prolonging breastfeeding led to reduced T1D risk, while early exposure increased the risk of islet autoimmunity and T1D risk in susceptible infants. The infants whose breastfeeding control group. Curiously, this may indicate a window of exposure to gluten in infancy outside of which islet autoimmunity and T1D risk in susceptible infants is increased. The study also found that if gluten-containing grains were introduced while the infant was still breastfeeding, the risk of islet autoimmunity and T1D was reduced, independent of the window of exposure previously calculated.

Administration of antibiotics such as doxycycline, fusidic acid, colistin and Bactrim to BBDP rats and NOD mice after weaning leads to the prevention of T1D development. Although the mechanism is not entirely understood, microbiota dysbiosis affects the development of T1D in both animal models. This is further supported by a study administrating probiotics to NOD mice which was found to induce IL-10 production, an immunoregulator and anti-inflammatory cytokine, and to prevent T1D development (Calcinaro et al., 2005). Another study revealed neonatal administration of an immunodominant epitope of T1D, peptide p277, proved to potentiate the protective effect of a hydrolysed casein diet, reducing the incidence of T1D by 64% or delaying its development (Brugman et al., 2004).

The jejunal of T1D sufferers have been found to display increased IFNγ and TNF-α, inflammatory response factors leading to pancreatic damage, their amounts correlating with the severity of the disease (Westerholm-Ormio et al., 2003). Significantly, a Th1 bias has been found in the mediastinal lymph node (MLN), a gut-associated secondary lymphoid organ where APCs present soluble dietary antigens to naïve T cells, of T1D individuals (Chakir et al., 2005). In healthy individuals, the gut mucosa is a Th2 predominant environment which allows for normal immunosuppressive response to gluten. In T1D rats, however, a Th1 bias is apparent, resulting from a Th2-specific Gata3 deficit causing an imbalance in Th1/Th2 differentiation. Elevated Th1 levels results in increased IFNγ and TNF-α production leading to pancreatic islet β-cell damage. Chakir and his team also found gluten-specific CD4+ T cells in the MLN of early-stage diabetic rats. Low frequencies of the cells were found in the spleen, suggesting activation of CD4+ T cell in the gut. This experiment links the gut immune system and T1D.
Bosi et al. (2006) showed increased intestinal permeability to precede T1D. He studied 81 subjects with islet autoimmunity at varying stages (preclinical, newly-onset and long-term established diabetes) and 40 control subjects and submitted them to the lactulose–mannitol test. Orally administered, the two sugars were measured in urine to extrapolate intestinal permeability. Disaccharide lactulose, a larger molecule, crosses the intestinal epithelium intracellularly via TJs while monosaccharide mannitol, a smaller molecule, is transported across the epithelium transcellularly through water-filled pores on the cell membrane. Altered intestinal anatomy or functional integrity would result in facilitated passage of one or both molecules. Intestinal permeability to lactulose was shown to be elevated in all islet autoimmunity individuals indicating barrier damage while integral surface mucosa remaining intact shown by unchanged permeability to mannitol compared to controls, thus increasing the lactulose:mannitol ratio. This study supports the hypothesis that increased intestinal permeability precedes T1D.

The morphological aspect of the intestinal mucosa in non-coeliac T1D individuals was studied by Secondulfo et al. (2004) to investigate reasons for increased permeability. Four parameters of the mucosal ultra-structural were evaluated: microvilli height, microvilli thickness, distance between microvilli, and TJ thickness. Reduced density, displacement and abnormal (short and thin) formation of microvilli were found on the apical membrane enterocytes, many of which contained large vacuoles, engorged mitochondria and a surplus of lysosomes. Enterocyte intercellular spaces were enlarged and TJ domains were displaced and thickened. The disturbed intestinal epithelium function in non-coeliac T1D individuals was associated with altered mucosal morphology suggesting loss of function of the intestinal barrier leading to pathogenesis.

A wide collection of studies demonstrate synergism between microbiota dysbiosis, increased intestinal permeability, altered mucosal immunity and pathogenesis of T1D. Kuitunen et al. (2002) found an increased lactulose and mannitol absorption in T1D sufferers thought to be due to altered intestinal permeability (Kuitunen et al., 2002, Secondulfo et al., 2004, Sapone et al., 2006). Increase in absorption of the two sugars was also found to be the case for β-cell autoimmune individuals suggesting altered intestinal permeability prior to the onset of T1D (Bosi et al., 2006). Histological changes in height and thickness of intestinal villi as well as their spacing and TJ assembly was altered in T1D individuals signifying the presence of mucosal injury (Secondulfo et al., 2004). Structural changes in TJ complexes in T1D were understood from recordings of elevated plasma zonulin levels in individuals with T1D (Sapone et al., 2006). Several experiments have investigated intestinal biopsies in children with T1D and found elevated interleukin and interferon levels indicating intestinal inflammation (Savilahiti et al., 1999, Westerholm-Ormio et al., 2003). Auricchio and his team found heightened CD3+ and CD25+ cells and increased HLA gene expression in intestinal mucosal cells following exposure to gliadin in T1D individuals demonstrating intestinal T-cell activation by gliadin (Auricchio et al., 2004).

In conclusion, individuals with T1D are either genetically predisposed, have been subjected to environmental triggers or experienced gut microbiota dysbiosis and display increased intestinal permeability, heightened immune activation (e.g. inflammation), histological changes and elevated plasma zonulin. In contrast to coeliac disease with the sole trigger of gliadin, T1D is believed to have several environmental triggers; Bovine insulin, in cow milk, has been shown to elicit similar reactions to gliadin resulting in T1D development. Bovine insulin administration in infants may sensitize intestinal T-cells later partaking in pancreatic insulin-producing β-cell destruction, an autoimmune response. Evidently further research is necessary wholly to understand the role of the gut and its microbiota in T1D. However, it is understood that microbiota dysbiosis causes upregulation of gut and systemic inflammation, due to endotoxins from pathogenic bacteria or to pro-inflammatory cytokines synthesized by immune cells, and causes T1D as well as disrupting gut-brain axis communication potentially leading to neuroinflammation and cognitive dysfunction (e.g. Alzheimer’s) (Bhattacharjee and Lukiw, 2013). Identifying the particular environmental triggers and improving investigative methods will greatly help evaluate the intestinal epithelium and hopefully provide important insights towards better understanding the pathogenic process of the disease and consequentially potentiating prevention and treatment.

**Discussion**

As evidenced, autoimmune disorders develop over time and can be preclinically detected. Due to their ambiguous symptoms (fatigue, muscle or joint ache, general malaise), correct diagnosis of autoimmune disorders can prove difficult. Many autoimmune disease sufferers wait until symptoms aggravate and the disease begins to take its toll before seeking medical advice, at which stage disease reversal may no longer be possible.

The majority of autoimmune disorders are not well understood. Identification of the triad of triggers—genes, environmental factors and microbiota dysbiosis—as well as improvements of investigative techniques will allow better understanding of the pathological processes involved and permit treatment development. Understanding such functioning will allow prevention of disordered intercellular communication and digestive disorders leading to autoimmune diseases, tissue inflammation, harmful adaptations and metastasis. Remarkably, the same system which can cause such damage could also be the key to curing hundreds of diseases through tissue specific drug delivery.

Fasano unknowingly uncovered an innovative strategy for the delivery of drugs, macromolecules and vaccines across the
body’s various epithelia in an innocuous and minimally inflammatory manner. Interestingly, not only intestinal but extra-intestinal epithelia such as tracheobronchial and renal tubule, as well as the vascular endothelium including the blood brain barrier may be targeted.

Zonulin analogues, such as AT-1002, have been developed and promote tissue penetration of macromolecules across a wide variety of surfaces while preserving membrane integrity thus altering permeability in a non-destructive, transient and reversible manner. Multiple delivery routes mean facilitated administration of the vaccine or drug increasing patient compliance and appeal to practitioners. AT-1002 has been demonstrated on nasal epithelia, intestinal epithelia and cultured brain endothelial cells. It can be used to transport PEG or insulin across the intestinal epithelium for treatment of constipated or diabetic individuals (Fasano and Uzzau, 1997, Song, Fasano and Eddington, 2008). AT-1002 can also induce rapid and reversible permeability of the blood brain barrier and thus increase absorption of doxorubicin and paclitaxel for cancer treatment (Karyekar et al., 2003). The analogue also instigates protective immune responses by adjuvant mucosal antigen delivery when administered nasally or rectally (e.g. ovalbumin and tetanus toxoid (Marinaro et al., 2003)). Cyclosporine transported with AT-1002 is used in the prevention of transplant rejection, Crohn’s disease and rheumatoid arthritis. It has also been experimentally tested to treat aids (AT-1002 taken along with ritonavir and saquinavir) and viruses such as varicella, herpes genitalis and zoster (with acyclovir) (Salama et al., 2005).

To summarize, zonulin agonists can be used to reversibly increase paracellular transport of drug delivery with less toxicity than previous absorptive enhancers, while antagonists can be used to prevent increased absorption of pathogenic molecules or allergens. Zonulin agonists and antagonists have the potential for significant and effective use in pharmacology not only in autoimmune disorders but in all diseases.

In conclusion, we know significantly more today than we did 5 years ago and it is to be hoped that we may be able to say the same in 5 years’ time. The non-destructive opening of tight junctions means ‘open sesame’ to new therapies. Large long-term studies, however, are required to determine potential adverse effects of possible new therapeutic approaches. So far, the results look promising. Since it is now known that hyperpermeability precedes disease, a new and innovative approach to treatment, arresting the interplay between genes and environmental factors through intestinal barrier function re-establishment, can be used in prevention or treatment of autoimmune disorders.

Author biography

Graduated in 2016 with a First Class Honours in Physiology (BSc) from the University of Glasgow. Currently studying Radiotherapy & Oncology (MSc) at London South Bank University, graduating in 2018.

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